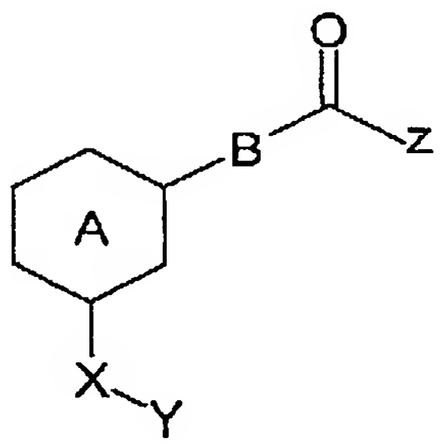
passive diffusion across plasma membranes or by active transport mechanisms. The BBB thus forms an effective barrier to many peripherally circulating substances.

An alternative method of excluding compounds from the brain is to incorporate structural features which enable them to be actively pumped across the BBB. One such example is the opioid agonist loperamide; although lipophilic, loperamide contains structural features recognized by the p-glycoprotein transporter (MDR1) that allow it to be actively pumped across the blood brain barrier. [Wandel, C. *et al*, *Anesthesiology* 2002, *96*, 913-920; Seelig, A. *et al*, *Eur. J. Pharm. Sci.* 2000, *12*, 31-40].

The present invention seeks to provide new cannabinoid receptor modulators. More particularly, the invention seeks to provide cannabinoid receptor modulators that alleviate and/or eliminate some of the disadvantages commonly associated with prior art modulators, for example undesirable psychoactive side effects. More specifically, though not exclusively, the invention seeks to provide modulators that selectively target peripheral cannabinoid receptors.

STATEMENT OF INVENTION

A first aspect of the invention relates to a compound of formula I, or a pharmaceutically acceptable salt thereof,



wherein

Z is OR^1 or NR^1R^2 wherein each of R^1 and R^2 is independently H, or a hydrocarbyl group;

X is an alkylene, alkenylene, or alkynylene group, each of which may be optionally substituted by one or more substituents selected from alkyl, COOH, CO_2-alkyl, alkenyl, CN, NH_2, hydroxy, halo, alkoxy, CF_3 and nitro;

Y is a polar functional group selected from OH, NO_2, CN, COR^3, $COOR^3$, NR^3R^4, $CONR^3R^4$, SO_3H, SO_2-R^3, $SO_2NR^3R^4$ and CF_3, where each of R^3 and R^4 is independently H or a hydrocarbyl group;

A is phenyl or pyridyl; and

B is $(CH_2)_n$ where n is 0;

with the proviso that:

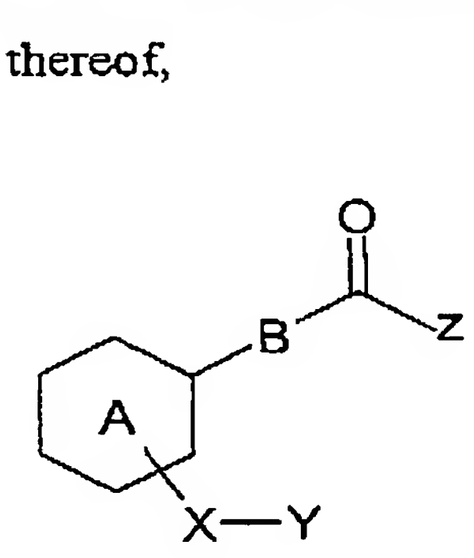
(i) when A is phenyl, and Z is OH, X-Y is other than C≡C-$(CH_2)_2$OH, C≡C-$(CH_2)_2$OH, C≡C-$(CH_2)_2CO_2$Me, $(CH_2)_4CO_2$H; and

(ii) when A is phenyl, and Z is OMe, X-Y is other than C≡C-$(CH_2)_4$OH; -$(CH_2)_4$-CHO, *cis*-CH=CH-$(CH_2)_3$OH, *trans*-CH=CH-$(CH_2)_3$OH;

and wherein the compound is other than 1-(N-octylcarbamoyl)methyl-3-carboxamidopyridinuim chloride, 3-methylcarbamoyl-1-dodecyloxycarbonylmethyl-pyridinium or 6-aminomethylpyridine-2-carboxylic acid ethyl ester.

Advantageously, the compounds of the present invention preferably exhibit improved aqueous solubility and/or decreased lipophilicity compared to prior art cannabinoid receptor modulators.

A second aspect of the invention relates to the use of a compound of formula Ia, or a pharmaceutically acceptable salt thereof,



Ia

wherein

Z is OR^1 or NR^1R^2 wherein each of R^1 and R^2 is independently H, or a hydrocarbyl group;

acid. Other examples of cannabinoids include anandamide, methanandamide and R(+)WIN55,212.

ENDOCANNABINOID

This term means a cannabinoid that exists naturally in the body – as opposed to an exogeneously supplied cannabinoid. Endocannabinoids are discussed by Di Marzo (1998) Biochimica et Biophysica Acta vol 1392 pages 153-175. An example of an endocannabinoid is anandamide. Teachings on this entity and anandamide amidase may be found in US-A-5874459. This document teaches the use of anandamide amidase inhibitors as analgesic agents.

CANNABINOID RECEPTOR

A cannabinoid receptor is any one or more of several membrane proteins that bind cannabinol and structurally similar compounds and mediate their intracellular action.

Two receptors for the psychoactive ingredient of marijuana Δ^9–tetrahydrocannabinol (THC), the CB1 and CB2 cannabinoid receptors, have been found (Pertwee 1997 Pharmacol Ther vol 74 129-180). Both of these receptors are seven-transmembrane-domain G-protein-coupled receptors. CB_1 receptors are found in the brain and testis. CB_2 receptors are found in the spleen and not in the brain.

For both types of receptor arachidonoylethanolamide (anandamide) is a putative endogenous ligand and both types are negatively coupled to adenylate cyclase decreasing intracellular cyclic AMP levels. Examples of sequences for such receptors are from *Mus musculus* – and include: CB1, database code CB1R_MOUSE, 473 amino acids (52.94 kDA); CB2, database code CB2R_MOUSE, 347 amino acids (38.21 kDa). More details on CB1 and CB2 now follow.

CANNABINOID RECEPTOR 1 (CB_1 or CNR1)

Background teachings on CB_1 have been presented by Victor A. McKusick *et al* on http://www.ncbi.nlm.nih.gov/Omim. The following information concerning CB_1 has

independently H or an alkyl group optionally substituted by one or more substituents selected from hydroxy, halo-, alkoxy-, nitro-, and a cyclic group.

For compounds of formula I, more preferably still, Y is selected from OH, CN, COOMe, COOH, $CONH_2$, CONHMe and $CONMe_2$.

For all the above embodiments, preferably each of R^1, R^2, R^3 and R^4 is independently H, an alkyl group, an aryl group, or a cycloalkyl group, each of which may be optionally substituted by one or more substituents selected from hydroxy, halo-, alkoxy-, nitro-, and a cyclic group.

In one particularly preferred embodiment of the invention for compounds of formula Ia, n is 0; i.e., B is absent and the -C(=O)Z moiety is attached directly to aryl group, A.

For compounds of formula I and Ia, preferably, X-Y is selected from

$-C\equiv C-(CH_2)_p-Y$;

$-C(R^5)=C(R^6)-(CH_2)_q-Y$; and

$-C(R^5)(R^6)C(R^7)(R^8)-(CH_2)_r-Y$;

where each of R^5, R^6, R^7 and R^8 is independently H or alkyl, and each of p, q and r is independently 1 to 6, more preferably, 2, 3, or 4.

For compounds of formula I and Ia, even more preferably, X-Y is selected from

$-C\equiv C-(CH_2)_p-Y$; and

$-CH=CH-(CH_2)_q-Y$;

where each of p and q is independently 1 to 6, more preferably 2, 3, or 4.

In one preferred embodiment, R^5 and R^6 are both H.

For compounds of formula I and Ia, in one especially preferred embodiment, X-Y is

cis $-C(R^5)=C(R^6)-(CH_2)_q-Y$

For compounds of formula I and Ia, in another preferred embodiment, X-Y is

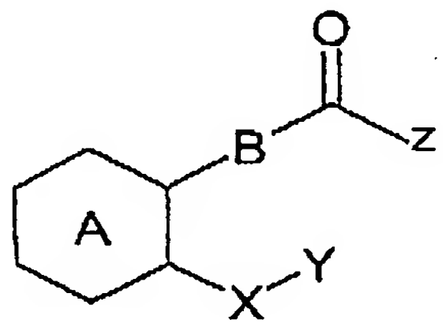
$-C(Me)_2-CH_2-(CH_2)_r-Y$ and r is 1 to 6, more preferably, 2, 3 or 4.

In another preferred embodiment, X-Y is $(CH_2)_s$-Y where s is 1 to 6, more preferably, 2, 3, 4 or 5.

Preferably, for compounds of formula Ia, A is an optionally substituted phenyl or pyridyl group, more preferably a phenyl group.

In another preferred embodiment, A is an unsubstituted phenyl or pyridyl group, more preferably an unsubstituted phenyl group.

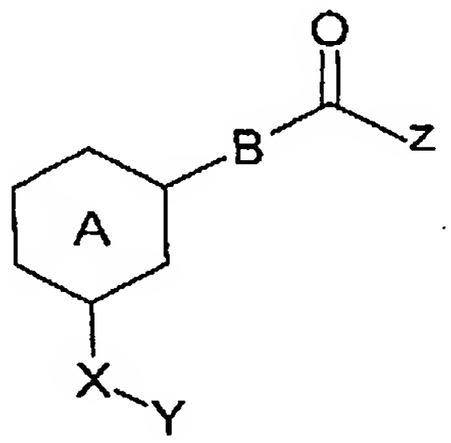
For compounds of formula Ia, in one particularly preferred embodiment, the compound is of formula Ib



Ib

wherein A, B, X, Y and Z are as defined above.

For compounds of formula Ia, in another particularly preferred embodiment, the compound is of formula Ic



Ic

wherein A, B, X, Y and Z are as defined above.

Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985).

Examples of suitable carriers include lactose, starch, glucose, methyl cellulose, magnesium stearate, mannitol and sorbitol. Examples of suitable diluents include ethanol, glycerol and water.

The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as, or in addition to, the carrier, excipient or diluent any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilising agent(s).

Examples of suitable binders include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, corn sweeteners, natural and synthetic gums, such as acacia, tragacanth or sodium alginate, carboxymethyl cellulose and polyethylene glycol.

Examples of suitable lubricants include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate and sodium chloride.

Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may be also used.

SALTS/ESTERS

The compounds of the invention can be present as salts or esters, in particular pharmaceutically acceptable salts or esters.

One aspect of the invention relates to a process comprising the steps of:

(a) performing an assay method described hereinabove;

(b) identifying one or more candidate compounds capable of modulating one or more cannabinoid receptors; and

(c) preparing a quantity of said one or more candidate compounds.

Another aspect of the invention provides a process comprising the steps of:

(a) performing an assay method described hereinabove;

(b) identifying one or more candidate compounds capable of modulating one or more cannabinoid receptors;

(c) preparing a pharmaceutical composition comprising said one or more candidate compounds.

Another aspect of the invention provides a process comprising the steps of:

(a) performing an assay method described hereinabove;

(b) identifying one or more candidate compounds capable of modulating one or more cannabinoid receptors;

(c) modifying said one or more candidate compounds capable of modulating one or more cannabinoid receptors;

(d) performing the assay method described hereinabove;

(e) optionally preparing a pharmaceutical composition comprising said one or more candidate compounds.

The above methods may be used to screen for a candidate compound useful as an modulators of one or more cannabinoid receptors, more preferably peripheral cannabinoid receptors.

REPORTERS

A wide variety of reporters may be used in the assay methods (as well as screens) of the present invention with preferred reporters providing conveniently detectable signals (eg. by spectroscopy). By way of example, a reporter gene may encode an enzyme which catalyses a reaction which alters light absorption properties.

Other protocols include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and fluorescent activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilising monoclonal antibodies reactive to two non-interfering epitopes may even be used. These and other assays are described, among other places, in Hampton R et al [1990, Serological Methods, A Laboratory Manual, APS Press, St Paul MN] and Maddox DE et al [1983, J Exp Med 15 8:121 1].

Examples of reporter molecules include but are not limited to (galactosidase, invertase, green fluorescent protein, luciferase, chloramphenicol, acetyltransferase, (glucuronidase, exo-glucanase and glucoamylase. Alternatively, radiolabelled or fluorescent tag-labelled nucleotides can be incorporated into nascent transcripts which are then identified when bound to oligonucleotide probes.

By way of further examples, a number of companies such as Pharmacia Biotech (Piscataway, NJ), Promega (Madison, WI), and US Biochemical Corp (Cleveland, OH) supply commercial kits and protocols for assay procedures. Suitable reporter molecules or labels include those radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors and magnetic particles. Patents teaching the use of such labels include US-A-3817837; US-A-3850752; US-A-3939350; US-A-3996345; US-A-4277437; US-A-4275149 and US-A-4366241.

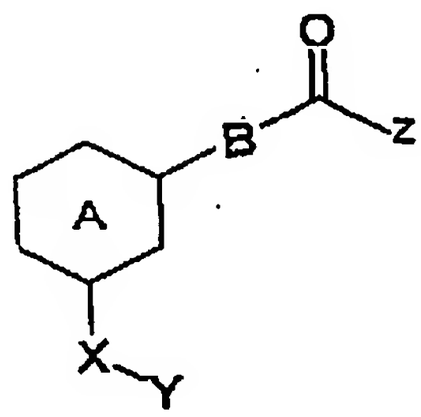
to hindlimb flexion using a strain gauge [Baker, D. *et al*, *Nature* 2000, *404*, 84-87]. Animals serve as their own controls and will be analysed in a pairwise fashion. To reduce the number of animals, effort and expense, following a drug–free period (spasticity returns within 24h) these animals receive different doses and or vehicle. Low doses of CB_1 agonists and CNS active CP55,940, as control, are locally (subcutaneous, intra-muscularly) administered into spastic ABH mice and the lack of activity in a contralateral limb analysed [Fox, A. *et al*, *Pain* 2001, *92*, 91-100]. Expression of CB_1 in the peripheral nervous system, including dorsal root ganglia, a non-CNS site for CB-mediated nociception can be removed using peripherin-Cre transgenic mouse [Zhou, L. *et al*, *FEBS Lett.* 2002, *523*, 68-72]. These conditional KO mice are maintained on the C57BL/6 background. These mice develop EAE following induction with myelin oligodendrocyte glycoprotein residues 35-55 peptide [Amor, S. *et al*, *J. Immunol.* 1994, *153*, 4349-4356].

In vivo evaluation in normal and CREAE mice

A CNS excluded compound provides a tool for examining if a component of a cannabinoid anti-spastic effect is mediated *via* peripheral CB receptors. Compound (16) was examined for CNS effects in normal mice as shown in Figures 2 and 3. At a dose of 1mg/kg no hypothermia or hypomotility was observed. In CREAE mice a marked effect on spasticity was noticed (Figure 4) providing strong evidence that a selective inhibition of spasticity is achievable without producing CNS effects. As stated above there is no established role for peripheral cannabinoid receptors in the control of spasticity, however, spasticity is likely to be a product of nerve damage in the spinal cord, at least in EAE, [Baker, D. *et al*, *FASEB J.* 2001, *15*, 300-302; Baker, D. *et al*, *J. Neuroimmunol.* 1990, *28*, 261-270] andaberrant signals to and from the musculature are likely, at least in part to contribute to the muscle spasms occuring in spasticity.

CLAIMS

1. A compound of formula I, or a pharmaceutically acceptable salt thereof,



wherein

Z is OR^1 or NR^1R^2 wherein each of R^1 and R^2 is independently H, or a hydrocarbyl group;

X is an alkylene, alkenylene, or alkynylene group, each of which may be optionally substituted by one or more substituents selected from alkyl, COOH, CO_2-alkyl, alkenyl, CN, NH_2, hydroxy, halo, alkoxy, CF_3 and nitro;

Y is a polar functional group selected from OH, NO_2, CN, COR^3, $COOR^3$, NR^3R^4, $CONR^3R^4$, SO_3H, SO_2-R^3, $SO_2NR^3R^4$ and CF_3, where each of R^3 and R^4 is independently H or a hydrocarbyl group;

A is phenyl or pyridyl; and

B is $(CH_2)_n$ where n is 0;

with the proviso that:

(i) when A is phenyl, and Z is OH, X-Y is other than C≡C-$(CH_2)_2$OH, C≡C-$(CH_2)_2$OH, C≡C-$(CH_2)_2CO_2$Me, $(CH_2)_4CO_2$H; and

(ii) when A is phenyl, and Z is OMe, X-Y is other than C≡C-$(CH_2)_4$OH; -$(CH_2)_4$-CHO, *cis*-CH=CH-$(CH_2)_3$OH, *trans*-CH=CH-$(CH_2)_3$OH;

and wherein the compound is other than 1-(N-octylcarbamoyl)methyl-3-carboxamidopyridinuim chloride, 3-methylcarbamoyl-1-dodecyloxycarbonylmethyl-pyridinium or 6-aminomethylpyridine-2-carboxylic acid ethyl ester.

2. A compound according to claim 1 wherein Y is selected from CN, OH, $COOR^3$, $SO_2NR^3R^4$, $CONR^3R^4$, where each of R^3 and R^4 is independently H or a hydrocarbyl group.

3. A compound according to any preceding claim wherein each of R^1,R^2, R^3 and R^4 is independently H, an alkyl group, an aryl group, or a cycloalkyl group, each of which may be optionally substituted.

4. A compound according to any preceding claim wherein Y is selected from OH, CN, $COOR^3$, $CONR^3R^4$, where each of R^3 and R^4 is independently H or an optionally substituted alkyl group.

5. A compound according to any preceding claim wherein Y is selected from OH, CN, COOMe, COOH, $CONH_2$, CONHMe and $CONMe_2$.

6. A compound according to any preceding claim wherein X-Y is selected from

$-C\equiv C-(CH_2)_p-Y$;

$-C(R^5)=C(R^6)-(CH_2)_q-Y$; and

$-C(R^5)(R^6)C(R^7)(R^8)-(CH_2)_r-Y$;

wherein each of R^5, R^6, R7, and R^8 is independently H or alkyl, and each of p, q and r is independently 2, 3, or 4.

7. A compound according to any preceding claim wherein X-Y is selected from

$-C\equiv C-(CH_2)_p-Y$; and

$-CH=CH-(CH_2)_q-Y$;

wherein each of p and q is independently 2, 3 or 4.

8. A compound according to claim 6 wherein X-Y is

cis-$C(R^5)=C(R^6)-(CH_2)_q-Y$ and q is 2, 3 or 4.

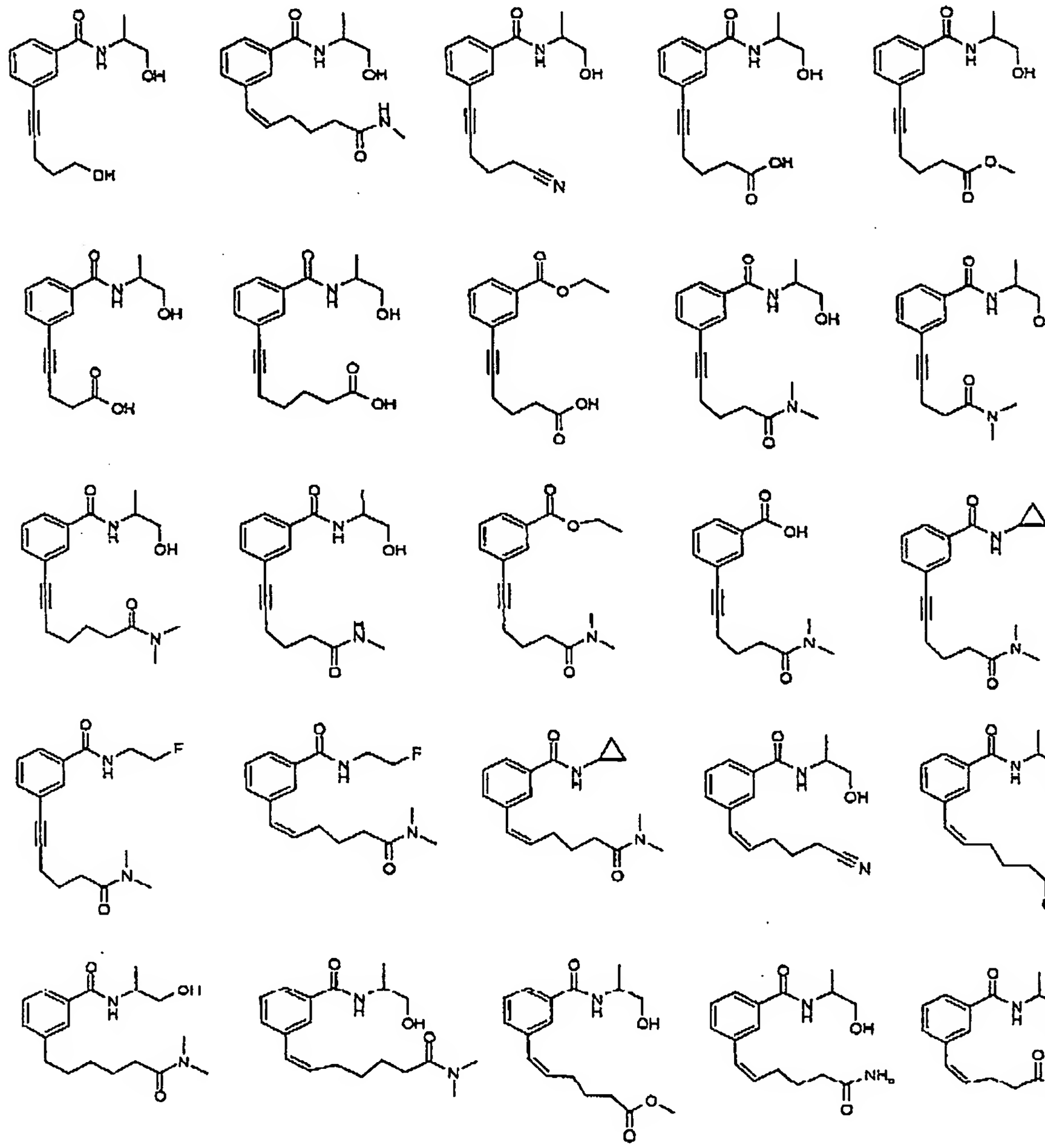
9. A compound according to any one of claims 1 to 6 or claim 8 wherein X-Y is $-C(Me)_2-CH_2-(CH_2)_r-Y$ and r is 2, 3 or 4.

10. A compound according to claim 1 wherein A is phenyl.

11. A compound according to any preceding claim wherein Z is OR^1 or NR^1R^2 and each of R^1 and R^2 is independently H, an alkyl or a cycloalkyl group, each of which may be optionally substituted by one or more OH or halogen groups.

12. A compound according to any preceding claim wherein Z is selected from OH, OEt, $NHCH_2CH_2F$, NH-cyclopropyl, $NHCH(Me)CH_2OH$ and $NHCH_2CH_2OH$.

13. A compound according to any preceding claim which is selected from the following:



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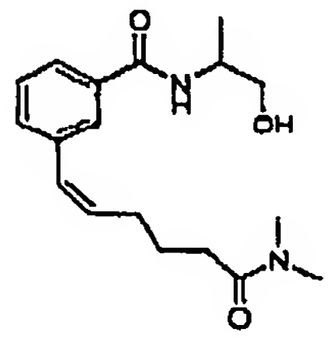
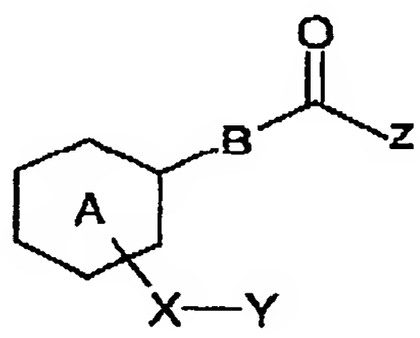
14. The compound of claim 13 which is



15. The compound of claim 14 which is in the form of a racemic mixture.

16. Use of a compound of formula Ia, or a pharmaceutically acceptable salt thereof,



Ia

wherein

Z is OR^1 or NR^1R^2 wherein each of R^1 and R^2 is independently H, or a hydrocarbyl group;

X is an alkylene, alkenylene, or alkynylene group, each of which may be optionally substituted;

Y is a polar functional group;

A is an aryl or heteroaryl group, each of which may be optionally substituted; and

B is $(CH_2)_n$ where n is 0, 1, 2, 3, 4 or 5;

in the preparation of a medicament for treating a muscular disorder.

17. Use according to claim 16 wherein the muscular disorder is a neuromuscular disorder.

18. Use of a compound of formula Ia, or a pharmaceutically acceptable salt thereof,

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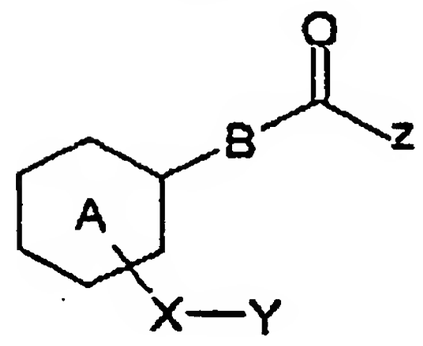


Ia

wherein

Z is OR^1 or NR^1R^2 wherein each of R^1 and R^2 is independently H, or a hydrocarbyl group;

X is an alkylene, alkenylene, or alkynylene group, each of which may be optionally substituted;

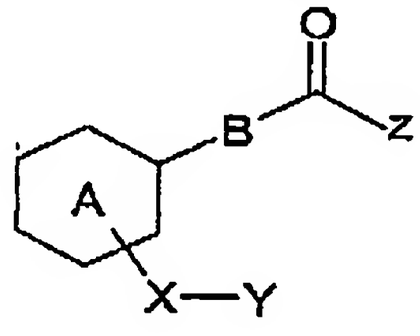
Y is a polar functional group;

A is an aryl or heteroaryl group, each of which may be optionally substituted; and

B is $(CH_2)_n$ where n is 0, 1, 2, 3, 4 or 5;

in the preparation of a medicament for controlling spasticity and tremors.

19. Use of a compound of formula Ia, or a pharmaceutically acceptable salt thereof,



Ia

wherein

Z is OR^1 or NR^1R^2 wherein each of R^1 and R^2 is independently H, or a hydrocarbyl group;

X is an alkylene, alkenylene, or alkynylene group, each of which may be optionally substituted;

Y is a polar functional group;

A is an aryl or heteroaryl group, each of which may be optionally substituted; and

B is $(CH_2)_n$ where n is 0, 1, 2, 3, 4 or 5;

in the preparation of a medicament for treating a gastrointestinal disorder.

20. Use according to claim 19 wherein the gastrointestinal disorder is a gastric ulcer.

21. Use according to claim 19 wherein the gastrointestinal disorder is Crohn's disease.

22. Use according to claim 19 wherein the gastrointestinal disorder is secretory diarroehea.

23. Use according to claim 19 wherein the gastrointestinal disorder is paralytic ileus.

24. Use according to any one of claims 16 to 23 wherein said modulator selectively modulates peripheral cannabinoid receptors.

25. Use according to any one of claims 16 to 24 wherein said compound selectively modulates peripheral cannabinoid receptors over central cannabinoid receptors.

26. Use according to any one of claims 16 to 25 wherein the compound binds substantially exclusively to peripheral cannabinoid receptors.

27. Use according to any one of claims 16 to 26 wherein the compound is a cannabinoid receptor agonist.

28. Use according to any one of claims 16 to 27 wherein the compound does not substantially agonise central cannabinoid receptors.

29. Use according to any one of claims 16 to 28 wherein the compound is substantially excluded from the CNS.

30. Use according to any one of claims 16 to 29 wherein Y is selected from NO_2, CN, OR^3, COR^3, $COOR^3$, NR^3R^4, $CONR^3R^4$, SO_3H, SO_2-R^3, $SO_2NR^3R^4$ and CF_3, where each of R^3 and R^4 is independently H or a hydrocarbyl group.

31. Use compound according to any one of claims 16 to 30 wherein Y is selected from CN, $COOR^3$, $SO_2NR^3R^4$, $CONR^3R^4$, where each of R^3 and R^4 is independently H or a hydrocarbyl group.

32. Use according to any one of claims 16 to 31 wherein the compound is as defined in any one of claims 1 to 15.

33. A method of treating a disorder associated with the modulation of peripheral cannabinoid receptors, said method comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 15.

34. A method according to claim 33 wherein said disorder is associated with peripheral cannabinoid receptor deactivation.

35 A method according to claim 33 or claim 34 wherein the compound does not substantially agonise central cannabinoid receptors.

36. A method according to any one of claims 33 to 35 wherein the compound binds substantially exclusively to peripheral cannabinoid receptors.

37. A method according to any one of claims 33 to 36 wherein the compound is substantially excluded from the CNS.

38. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable diluent, excipient or carrier.

39. Use of a compound of formula Ia, or pharmaceutically acceptable salt thereof, as defined in claim 16 in an assay for identifying further compounds capable of modulating cannabinoid receptor activity.

40. Use according to claim 39 wherein the assay is a competitive binding assay.